UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,800	07/22/2003	David Bebbington	VPI/00-129-3 DIV US	7445

27916 7590 09/03/2004

VERTEX PHARMACEUTICALS INC.
130 WAVERLY STREET
CAMBRIDGE, MA 02139-4242

EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,800	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,19-22 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-10,13,19,20,27 and 28* is/are allowed.

6)☐ Claim(s) *11,12,21,22 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 7/22/03. There are twenty claims pending and twenty under consideration. Claims 1-8 are compound claims. Claims 9 and 10 are composition claims. Claims 11-13, 19-22, and 26-28 are method of using claims. This is the first action on the merits. The application concerns some fused pyrimidyl N-1H-pyrazole compounds, compositions, and uses thereof.

Title

2. The title of the invention is no longer descriptive after restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: insertion of the phrase "Fused Pyrimidyl" at the beginning of the title.

Priority

3. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. Since the parent application has become a patent, the expression “now Patent No. 6,660,731” should follow the filing date of the parent application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify patients requiring "inhibiting GSK-3 or Aurora activity". It is unclear what diseases and treatments or which patients Applicants are intending to encompass. Identifying which diseases applicants intend these claims to cover will involve extensive and potentially inconclusive clinical research. Without such clinical research to identify the patients and diseases Applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Lines 14-22, page 17 defines "GSK-3 mediated condition" using open language. The diseases require only that "GSK-3 ... play a role". Does this mean GSK-1 up-regulation must be the causative factor, a resulting factor, or can it be incidental to the fundamental disease process? There follows a list of diseases with no underlying common mechanism. The paragraph spanning pages 101 to 102 and

the following paragraph describe inhibiting GSK-3 in a patient with formula IV but do not specify which patients are to be treated. What is intended here?

Lines 19-27, page 18 defines "aurora-2-mediated condition" using open language "without limitation". Is this the same as aurora or is aurora-2 a distinct protein kinase? The condition requires only that "aurora-2 ... play a role". Does this mean aurora-2 up-regulation must be the causative factor, a resulting factor, or can it be incidental to the fundamental disease process? Cancer, specifically colon and ovarian cancer, is the only named disease. Are there others? Lines 29, page 102 to line 8, page 103 describe Aurora inhibition in connection with formula IV but do not specify which patients require its inhibition. Colon, ovarian, and now breast cancer are mentioned specifically. Are these three the only disease treatments covered in claim 11 or are there others?

5. Claims 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify patients requiring "inhibiting the production of hyperphosphorylated tau protein". It is unclear what diseases and treatments or which patients Applicants are intending to encompass. Identifying which diseases applicants intend these claims to cover will involve

extensive and potentially inconclusive clinical research. Without such clinical research to identify the patients and diseases Applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Lines 16-22, page 102 describe hyperphosphorylated Tau protein in connection with formula IV but do not specify which patients require its inhibition. Is Alzheimer's disease the only disease treatment covered in claim 21 or are there others? Lines 23-28, page 102 describe β-catenin phosphorylation inhibition in connection with formula IV but do not specify which patients require its inhibition. Is schizophrenia the only disease treatment covered in claim 22 or are there others?

Lines 19-27, page 18 defines "aurora-2-mediated condition" using open language "without limitation". Is this the same as aurora or is aurora-2 a distinct protein kinase? The condition requires only that "aurora-2 ... play a role". Does this mean aurora-2 up-regulation must be the causative factor, a resulting factor, or can it be incidental to the fundamental disease process? Cancer, specifically colon and ovarian cancer, is the only named disease. Are there others? Lines 29, page 102 to line 8, page 103 describe Aurora inhibition in connection with formula IV but do not specify which patients require its inhibition. Colon, ovarian, and now

breast cancer are mentioned specifically. Are these three the only disease treatment covered in claim 23 or are there others?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 21, 22, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes, schizophrenia, colon, ovarian, and breast cancer, does not reasonably provide enablement for treating all patients requiring "inhibiting GSK-3 or Aurora activity", "inhibiting the production of hyperphosphorylated tau protein", or the other listed cancers. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re*

Rainer, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The three main issues are the correlation between clinical efficacy for the claimed treatments and Applicants' four *in vitro* assays, the state of the art, and the breadth of the claims.

a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating the claimed diseases is found in the passage spanning line 14, page 17 to line 29, page 22, which merely states Applicants' intention to do so. Applicants describe formulations in are taught in the passage spanning line 18, page 23 to line 2, page 27. Doses required to practice their invention are described in 21-28, page 28. A 10,000-fold range of doses is recommended. Since no GSK-3 or Aurora-2 inhibitor has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* assay, drawn to inhibition of the GSK-3 enzyme, described in the passage spanning line 29, page 333 to line 33, page 335. There is an *in vitro* assay,

drawn to inhibition of the Aurora-2 enzyme, described in the passage spanning line 1, page 336 to line 14, page 337. There is an *in vitro* assay, drawn to inhibition of the ERK-2 enzyme, described in lines 6-25, page 338. There is an *in vitro* assay, drawn to inhibition of the Src kinase enzyme, described in the passage spanning lines 24, page 339 to line 31, page 341. Applicants do not assert and it is not art recognized that activity in these four *in vitro* assays are correlated to clinical efficacy for treating any diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease with Applicants' kinase enzyme inhibitors, which involves physiological activity. e) The state of the tau protein hyperphosphylation pharmaceutical art is summarized by Heutink (Hum Mol Genet.) who states that the relationship between tau protein and neurodegenerative disease in unclear, first complete paragraph page 984. In the final sentence of the cited paragraph direction for future research is proposed, implying that such inhibitors were not, as of 2000, known to be useful for treating dementia. Fisher (Therapeutic strategies in Alzheimer's disease: M1 muscarinic agonists.) states in the first paragraph, column 1, page 105 that M1 subtype of muscarinic agonists can reduce excess phosphorylation of Tau protein. Yet in the final paragraph on the cited page, he admits that such agonists have failed in clinical trials of Alzheimer's disease.

While compounds working by Applicants proposed mechanism of action might well turn out to be effective for the treatment of AD after additional research, as of 2000, the skilled clinician did not know how to use them for such purposes. The state of the clinical arts in GSK-3 diseases is provided by Eldar-Finkelman (Expert Opinion on Investigational Drugs). Eldar-Finkelman (Expert Opinion on Investigational Drugs) staes in the conclusion on page 1516 that diabetes treatment is a possible use of GSK-3 inhibitors.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown list of diseases embraced by the terms patients requiring "inhibiting GSK-3 or Aurora activity" and patients requiring "inhibiting the production of hyperphosphorylated tau protein". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

6. Claims 1-10, 13, 19, 20, 27, and 28 are allowed.

Conclusion

7. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

8. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703)

872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624
(703) 272-0670

TCMcK/me